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FREQUENCY OF AMINOGLYCOSIDES RESISTANCE GENES (ANT(4')-IA, APH(3')-IIIA, AAC-(6')-IE-/APH]2) IN STAPHYLOCOCCUS AUREUS ISOLATED FROM SURGICAL AND RESPIRATORY SITE INFECTIONS

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Abstract

Background: *Staphylococcus aureus is the most common bacterial cause of surgical wound infections. Aminoglycoside antibiotics are often used in combination with beta-lactams or glycopeptides to treat Staphylococci. The main mechanisms of resistance to aminoglycosides in staphylococcal species include aminoglycoside acetyltransferases AACs, aminoglycoside phosphoryltransferase APHs, aminoglycoside nucleotidyltransferases ANTs. The purpose of the present study is to determine the frequency of [aac (6')-Ie-aph (2')], ant (4')-Ia, and aph (3')-IIIa genes encoding aminoglycoside modifying enzymes by PCR method in Staphylococcus aureus isolated from surgical wounds.*

Materials and methods*: In the present study, 77 isolates of Staphylococcus aureus were collected from patients with surgical wound and respiratory site infections hospitalized in Yasuj hospitals. Antibiotic sensitivity pattern was determined by disc diffusion method according to CLSI guidelines for gentamicin, kanamycin, tobramycin, amikacin, and neomycin antibiotics. PCR method was used to identify aminoglycoside resistance genes ant(4')-Ia, aph(3')-IIIa, aac-(6')-Ie-/aph]2.*

Findings*: The highest rate of resistance to aminoglycosides was 68.8% amikacin, 64.9% gentamicin, 64.9% tobramycin, 61% kanamycin, and 57.1% neomycin. The frequency of aminoglycoside antibiotic-resistance genes (ant(4')-Ia, aph(3')-IIIa, aac-(6')-Ie-/aph]2) in isolates resistant to amikacin antibiotic respectively 13.2%, 18.6%, and 16.4% were reported.*

Conclusion*: Due to the increase in the prevalence of antibiotic resistance during the clinical use of these drugs, Fast diagnosis and timely identification of resistant strains seem essential in order to choose appropriate treatment options and prevent the spread of resistance. Therefore, the identification of aminoglycoside antibiotic-resistance genes can play an important and effective role.*

Keywords: *staphylococcus aureus, [aac (6')-Ie-aph (2")], ant (4')-Ia and aph (3')-II*I

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Introduction

Staphylococcus aureus bacteria is one of the nosocomial opportunistic infectious agents that causes various diseases such as abscess, blood infection, infection after surgery, and sometimes death. This bacterium is gram-positive, catalase-positive, facultative anaerobic, and has no spores present in the anterior part of 20% of people *[Kazemi et al., 2017]* In the group of staphylococci, coagulase-negative staphylococci are amongst the most important pathogens in causing infections caused by the use of hospital catheters and sanitary tampons [*Bokaeian et al., 2017*] . Surgical site infections [SSI] are amongst the most important nosocomial infections that lead to increased costs and mortality [*Shirani and Khodsiani 2022*] . The optimal use of aminoglycosides in ICU settings requires balancing their rapid bactericidal activity against Gram-negatives with their toxicity profile, while accounting for the unique pharmacokinetics of critically ill patients [*Fallahi et al., 2022*]. Surgical wound infections are the second most common cause of hospital-acquired infections in hospitalized patients [*Salahuddin et al., 2022*]. And together they cause at least 17 percent of all hospital infections [*Brunicardi et al., 2019*].

Aminoglycoside antibiotics are used in combination with beta-lactam antibiotics to treat many infections of staphylococcal origin [*Hu et al., 2015*] . The treatment of these infections with a wide range of antibiotics has caused resistance and emergence of new strains [*Zuo et al., 2014*] . Resistance to aminoglycoside antibiotics is based on three main mechanisms: a change in the ribosomal binding site of the drug, a decrease in drug permeability, and enzymatic inactivation of the drug [*Hu et al., 2015*] . Enzymatic inactivation of aminoglycoside antibiotics by aminoglycoside modifying enzymes is one of the main resistance mechanisms in staphylococci species [*Ida et al., 2001*] . The basis of the classification of these enzymes is their changing activity, which is divided into three categories: aminoglycoside acetyltransferase, aminoglycoside phosphoryltransferase, and aminoglycoside nucleotidyltransferase [*Couto et al., 1996; Fatholahzadeh et al., 2009].*Three enzymes AAC(6′)/APH(2″), H and (3′)-III APH and ANT(4′), which are respectively encoded by aac(6')-Ie-aph(2'')-I genes, aph(3')-IIIa, and ant(4')-Ia are among the most common modifying enzymes in various staphylococcal species, which are of great therapeutic and clinical importance [*Malek Hosseini et al., 2016*] .

Considering the role of Staphylococcus aureus in causing surgical site infections, and the increasing importance of antibiotic resistance in bacteria and since the pattern of drug resistance has geographical, regional, and even hospital distribution, therefore determining the resistance pattern of staphylococcal strains isolated from surgical site infections by phenotypic method and determining its genetic factors in these strains can help in determining the appropriate treatment regimen for patients and presenting the results to the infection control committees of hospitals in terms of The control of multi-resistant strains as well as epidemiological studies should be effective. The present research aims to determine the amount of antibiotic resistance and frequency of aminoglycoside antibiotic-modifying enzyme genes on Staphylococcus aureus samples isolated from surgical wound infections in the city of Yasuj.

Materials and methods

In this cross-sectional study during one year, 77 clinical samples of surgical site infections were collected from patients hospitalized in Yasuj hospitals. Patients who were hospitalized for a long time and were suspected of bacterial infection were considered. Phenotypic identification of Staphylococcus aureus isolates by gram staining, catalase, coagulase tests, and culture on mannitol salt agar (Merck, Germany) was done. The confirmed isolates were stored in a TSB medium with glycerol and stored at -20°C until the next tests.

Phenotypic identification of Staphylococcus aureus and antibiotic susceptibility testing.

Antibiotic resistance was investigated based on CLSI standard protocol and using the Bauer-Kirby disc diffusion method. In this investigation, antibiotics gentamicin (10 µg), amikacin (30 µg), tobramycin (30 µg), neomycin (30 µg), and kanamycin (30 µg made in the USA) were used. According to CLSI instructions, first, Mueller-Hinton Agar medium (Conda, Spain) with a diameter of 4-6 *mm* was made in 10 *cm* plates, and a bacterial suspension equal to the turbidity of half McFarland was

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Table 1.

Sequence of primers used for PCR amplification of aminoglycoside resistance genes aac(6')-Ie-aph(2'')-I, aph(3')-IIIa and ant(4')-Ia:

Gene	Primer	The size of the reproduced piece (base pair)	source
aac(6')-Ie aph(2'')	F-CAGGAATTTATCGAAAATGGTAGAAAAG R- CACAATCGACTAAAGAGTACCAATC	369	*Rahimi et al., 2007*
aph(3')-IIIa	F-GGCTAAAATGAGAATATCACCGG R-CTTTAAAAAATCATACAGCTCGCG	523	*Rahimi et al., 2007*
ant(4')-Ia	F-CAAACTGCTAAATCGGTAGAAGCC R-GGAAAGTTGACCAGACATTACGAACT	294	*Agudelo et al., 2014*

made and its turbidity was read at a wavelength of 620 nm by a spectrophotometer (JENWAY-632D, China) and was used in the antibiogram test. The sample was cultured on Muller-Hinton agar medium using a sterile swab, and the antibiotic discs were placed at 13 *mm* distances from each other on Mueller-Hinton agar medium and incubated for 24 hours at 37 degrees Celsius, and then the diameter of the non-growth halo specific to each antibiotic was measured with a ruler, and the antibiotic sensitivity and resistance of each bacterium was determined [*Sabzevar et al., 2016*].

PCR reaction to detect aac(6')-Ie-aph(2'')-I, aph(3')-IIIa and ant(4')-Ia genes.

The boiling method was used for DNA isolation [Ahmed, Dablool 2017]. It should be noted that all steps were performed in sterile conditions and sterile tubes. In order to identify and multiply the coding genes for resistance aac(6')-Ie-aph(2'')-I, aph(3')-IIIa and ant(4')-Ia, the primers mentioned in Table 1 were used. Each PCR reaction was performed in a final volume of 25 microliters (O-SM Master Mix - China, 0.1 micromole reverse primer, distilled water, and 2.5 microliters of sample DNA). These materials were mixed in a microtube and then placed in a thermocycler (BIO-RAD t100-Singapore) according to table 2. The PCR products were electrophoresed on a 1% agarose gel, visualized under UV light after DNA safe staining and documented in Gel Documentation System (Major science, Taiwan).

Table 2.

Cycle number, temperature, and time for the amplification of aminoglycoside resistance genes aac(6')-Ie-aph(2'')-I, aph(3')-IIIa and ant(4')-Ia

	Time (*Seconds*)	Temperature (°C)
Initial Denaturation	300	94 °C
Denaturation	45	94 °C
Annealing	45	58 °C
Extension	45	72 °C
Final Extension	300	72 °C

Data analysis

The data obtained from the study were analyzed using SPSS 19 software. For this purpose, descriptive statistical methods (determining frequency, percentage, and average) and analytical (chi-square test) were used. The significance level of the data was considered $p \leq .05$.

Results

In the present study, which was investigated on 77 samples of Staphylococcus aureus isolated from surgical site infections from Imam Sajad and Shahid Beheshti hospitals in Yasuj city, the results of antibiotic resistance in the study showed that the highest rate of antibiotic resistance was Amikacin 53 (68.8%), followed by tobramycin 50 (64.9%), gentamicin 50 (64.9%) and kanamycin 47 (61%) neomicin 44 (44%) (table 3).

Generally, the most abundant aminoglycoside resistance gene among the studied Staphylococcus aureus isolates was related to aph (3')-IIIa with 27.3 (21% of isolates).

Examining the simultaneous presence of studied resistance genes showed that all three genes(aac-(6')-Ie-/aph2 + aph (3')-IIIa + ant (4')-Ia) in 1.3% of isolates (1 isolate), aph(3')-IIIa + ant (4')-Ia genes in 2.6% isolates (2 isolates) and aac-(6')-Ie-/aph2+ aph (3')-IIIa genes in 3.9% isolates (3 isolates) were simultaneously observed (figure1).

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Table 3.

Frequency of aminoglycoside resistance genes aac(6')-Ie-aph(2'')-I, aph(3')-IIIa and ant(4')-Ia based on antibiotic resistance

Antibiotic-resistant isolates	Gene	Abundance
Amikacin n=53	aac-(6')-Ie-/aph2	7 (13.2%)
	aph (3')-IIIa	14 (26.4%)
	ant (4')-Ia	10 (18.9%)
Tobramycin n=50	aac-(6')-Ie-/aph2	12 (24%)
	aph (3')-IIIa	12 (24%)
	ant (4')-Ia	9 (18%)
Gentamicin n=50	aac-(6')-Ie-/aph2	7 (14%)
	aph (3')-IIIa	16 (32%)
	ant (4')-Ia	7 (14%)
Kanamycin n=47	aac-(6')-Ie-/aph2	9 (20.5%)
	aph (3')-IIIa	12 (27.3%)
	ant (4')-Ia	11 (25%)
Neomycin n=44	aac-(6')-Ie-/aph2	9 (20.5%)
	aph (3')-IIIa	12 (27.3%)
	ant (4')-Ia	11 (25%)

Discussion

Staphylococcus aureus is an important pathogen in causing many infections. This bacterium is one of the main causes of hospital infections, including surgical site infections, which today has acquired resistance to a wide range of antibiotics, including β-Lactam, aminoglycosides, tetracyclines, etc. Aminoglycoside antibiotics are often used in combination with β-Lactam and glycopeptides in the treatment of staphylococcal infections. These antibiotics interfere with the synthesis of bacterial cell proteins by binding to the S 30 ribosomal subunit.

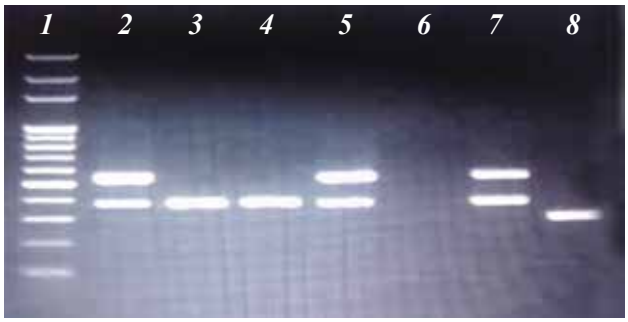

Figure 1. *Multiplex PCR for detection of Aminoglycoside resistance genes. 1; 100bp DNA size marker, lane 2; Positive control, lane 3 and 4; aac-(6')-Ie-/aph2 gene, lane 5, 7; aph (3')-IIIa and aac-(6')-Ie-/aph2 genes with bandwidths of 369 and 523, lane 6; Negative control, lane 8; ant gene (4')-Ia + IIIa with bandwidths of 294.*

Among the three action mechanisms of these antibiotics, the enzymatic deactivation of aminoglycosides by aminoglycoside modifying enzymes is the main mechanism of resistance to these drugs in staphylococcal species [*Ida et al., 2001; Pokrovskaya and Baasov 2010*]. In the present study, out of 77 isolates of Staphylococcus aureus isolated from surgical site infections, a total of 53% of Staphylococcus aureus samples [68 isolates] were resistant to one of the aminoglycoside antibiotics [kanamycin, gentamicin, neomycin, tobramycin, and amikacin]. The rates of antibiotic resistance to kanamycin, gentamicin, neomycin, tobramycin, and amikacin antibiotics were 64.9%, 64.9%, 57.1%, 64.9%, and 68.8%, respectively, and these results are consistent with the study of seyedi Marghaki and colleagues [*Malek Hosseini et al., 2016*]. In Khosravi's study in Ahvaz, the resistance ratios of gentamicin, amikacin, kanamycin, tobramycin, and neomycin antibiotics were reported as 84%, 77%, 86%, 82%, and 92%, respectively [*Khosravi et al., 2017*]. Also, in the study of Malek Hosseini et al., the rates of resistance to amikacin, tobramycin, and gentamicin were 76.5% [*Malek Hosseini et al., 2016*]. The rates of resistance to aminoglycoside antibiotics in the above studies were higher than the present study and did not agree with the present study. In the study by Almayahi et al., the rate of resistance to aminoglycoside antibiotics kanamycin, tobramycin, gentamicin, and amikacin were 28%, 25%, 22%, and 19%, respectively [*Al-Mayahi, Srhan, 2021*]. Also in the studies of *Abiri et al., Hawichild et al., and Al-Saadi et al.,* the levels of resistance to aminoglycoside antibiotics were lower than in the present study and they were not consistent with the present study. Due to the increase in the prevalence of resistance to aminoglycoside antibiotics in parallel with excessive and indiscriminate clinical use of these drugs, quick and timely diagnosis of resistant strains is essential in order to choose appropriate treatment options and prevent the spread of resistance [*Hauschild et al., 2008; Abiri et al., 2017; Al-Saadi and Abd Al-Mayahi 2021*].

The results of the analysis of aminoglycoside resistance genes in the present study showed that ant(4′)-Ia and aph(3′)-IIIa, aac(6′)-Ie/aph(2″) genes were identified respectively in 20.8%, 27.3% and 18.2% of Staphylococcus aureus isolates. In

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the present study, the frequency of aph(3′)-IIIa gene in the present study was 27.3%, which is more than the studies of Marghaki (15.7%), and Bokaeian (16.8%), but it is less than Rahimi's studies (38%), Khosravi (42%) and Turutoglu (25%) [*Turutoglu et al., 2009, Bokaeian et al., 2017; Khosravi et al., 2017; Marghaki et al., 2017; Rahimi, and Katouli 2020*] was less. The results of the present study showed that the ant(4′)-Ia gene was observed in 18.2% of Staphylococcus aureus isolates, which was more frequent than Khosravi's 11.8% and Marghaki's 12.2% studies. But compared to Rahimi's studies, 59%, Bekaian's had a lower prevalence of 19.5% *[Bokaeian et al., 2017; Khosravi et al., 2017; Qasemi et al., 2020*]. Also, these two resistance genes ant(4′)-Ia and aph(3′)-IIIa were not detected in any of the Staphylococcus aureus isolates in the study of Al-Saadi [*Al-Saadi,Abd Al-Mayahi, 2021*]. The results of the presence of the aac(6′)-Ie/aph(2″) resistance gene in the present study showed that this gene had the highest frequency of 20.8% among the studied Staphylococcus aureus isolates. Compared to the studies of Kavusi, Khosravi, and Omwenga et al., 2021 it was less frequent [*Khosravi et al., 2017; Kavusi et al., 2019; Omwenga et al., 2021*]. In terms of the simultaneous presence of genes, all three genes ant(4′)-Ia and aph(3′)-IIIa, aac(6′)-Ie/aph(2″) were observed simultaneously in 1.3% of the isolates. ant(4′)-Ia and aph(3′)-IIIa genes were observed simultaneously in 2.6% of the isolates, the simultaneous presence of these two genes was 4.2% in the study of Goudarzi et al., which was more than the present study. aph(3′)-IIIa, aac(6′)-Ie/aph(2″) genes were observed simultaneously in 3.9% of the studied isolates were observed, which was 36.3% less than the studies of Hosseini and 5.3% less than Goudarzi's study [*Hosseini et al., 2016; Mahdiyoun et al., 2016*].

The difference in the results of this study with other studies is due to the difference in the amount of antibiotic resistance among countries, hospitals, hospital departments, and even between different people in the studies. This variety of data in different studies can be related to the amount of antibiotic use and cultural variation in the use of antibiotics, the occurrence of different mechanisms of resistance, the selection and spread of resistant clones under the pressure of antibiotic use, the difference in the immune system of patients in various studies, and the difference in the health and treatment status in many studied areas. Such studies can lead to the identification of the resistance pattern of each region and hospital, methods of infection control, preventing the spread of resistance, and choosing appropriate treatment methods to rid patients of infections caused by resistant isolates of Staphylococcus aureus. Due to the increase in the prevalence of resistance to aminoglycoside antibiotics, in parallel with the excessive and indiscriminate clinical use of these drugs, it seems necessary to quickly and timely detect resistant strains in order to choose appropriate treatment options and prevent the spread of resistance, so identifying aminoglycoside antibiotic resistance genes can play an important and effective role. As a result, genetic transmission can be prevented by modifying the antibiotic prescription pattern and not using various antibiotics in treatment. It can also be concluded that using different antibiotics from different classes simultaneously can cause the emergence of multi-antibiotic-resistant strains.

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